The Value of Laboratory Tests for the Screening and Recognition of Alcohol Abuse in Primary Care Patients

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Background. Although alcohol abuse is prevalent in family practice, the diagnosis is not easily established. Laboratory tests are usually heavily relied on in the diagnostic process.

Methods. The value of laboratory tests for the screening and recognition of problem drinking in family practice is summarized, based on a review of the literature. A distinction is made between studies in selected populations of drinkers and studies in nonselected populations, ie, family practice.

Results. The most sensitive laboratory tests associated with excessive alcohol intake include γ-glutamyl transferase (GGT), mean corpuscular volume, and the ratio of alanine aminotransferase to aspartate aminotransferase. No single laboratory test or combination of tests is shown to be appropriate for screening. The positive predictive value for GGT is only about 25% in a population that has a 10% prevalence of problem drinking and increases to about 55% in a population that has a 30% prevalence of problem drinking.

Conclusions. Guidelines for the recognition of problem drinking in family practice should include elevated laboratory test values as one of the "alerting factors" for problem drinking, and not as a confirmation of a suspicion of problem drinking. In monitoring treatment response, GGT may be a powerful patient-motivating factor.

Key words. Alcoholism; diagnosis, laboratory; mass screening; family practice. (*J Fam Pract 1993; 37:268-276*)

The subject of this paper is the value of the laboratory tests for the screening, recognition, and management of problem drinking in family practice, based on a review of the literature. *Problem drinkers* are defined as those using alcohol to an extent that results in physical, social, or mental impairment.

The problematic use of alcohol is commonly seen in patients in family practice. Studies of patients visiting family physicians have revealed a prevalence rate of 6% to 15%.[1-3] Although problem drinkers have been shown to contact their family physician more frequently than controls,[4] they are not always recognized as such. The rate of recognition of problem drinkers by their family physicians ranges from 35% to 55%.[5-7]

To facilitate the screening and recognition of problem drinking, there has been a search for an objective biological marker that will indicate problem drinking if measurements deviate from expected values.[8-11] The presence of alcohol in urine, serum, and saliva can be easily assessed.[12] The relevance of these tests, however, is uncertain. Only a weak correlation between blood alcohol concentration and alcohol-related problems or diagnoses in the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) of alcohol abuse and dependence was shown to be present in a study of people who were arrested for driving while intoxicated.[13] Laboratory tests in which elevated values are associated with chronic excessive alcohol intake include γ-glutamyl transferase (GGT), alanine aminotransferase (ALT, formerly SGPT), aspartate aminotransferase (AST, formerly SGOT), lactate dehydrogenase, alkaline phosphatase, total bilirubin, cholesterol, triglycerides, uric acid, and mean corpuscular volume (MCV).[14,15] Among these, GGT, MCV, AST, and the AST/ALT ratio

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Table 1. Laboratory Tests in Selected Patient Populations (Alcoholics and Controls)

Primary Author/Year	Population Under Study	Test	Positivity Criterion	Sensitivity, %	Specificity, %
Kawachi 1990[18]	*Drinkers* (n = 64): alcoholic patients in detoxification unit, consumption >200 g alcohol per day for at least 2 weeks *Controls* (n = 88): patients with nonalcoholic liver diseases	GGT AST/ALT MCV	>100 IU/L >1.00 >90.0 fL	61 87 87	53 85 75
Behrens 1988[19]	*Drinkers* (n = 105): known alcoholic patients, consumption >50 g alcohol per day for at least 1 month *Controls* (n = 138): (1) alcoholics who had been abstinent for at least 6 weeks (n = 59); (2) patients with nonalcoholic liver diseases (n = 64), consumption ≤50 g alcohol per day; (3) healthy subjects with either no or only occasional alcoholic consumption (n = 15)	GGT MCV	>65 IU/L >100 fL	59 25	50 95
Kapur 1989[20]	*Drinkers* (n = 22): self-confessed alcoholics, 15 of them admitted to hospital for alcohol withdrawal, consumption >80 g alcohol per day for at least 3 weeks *Controls* (n = 153): (1) patients with alcoholic liver disease, consumption <50 g alcohol per day (n = 68); (2) patients with nonalcoholic liver diseases, consumption <20 g alcohol per day (n = 47); (3) patients without liver disease, consumption <20 g alcohol per day (n = 38)	GGT AST/ALT MCV	≥45 IU/L >2.00 ≥98 fL	90 19 65	37 96 82
Kwoh-Gain 1990[21]	*Drinkers* (n = 26): alcoholic subjects admitted for detoxification, consumption >80 g alcohol per day in previous 6 months *Controls* (n = 37): (1) healthy volunteers (n = 16); (2) patients with nonalcoholic liver diseases (n = 21), consumption <40 g alcohol per day in preceding 2 weeks	GGT AST AST/ALT MCV	>50 IU/L >40 IU/L >1.00 unknown	69 69 69 73	59 68 46 76
Stamm 1984[22]	*Drinkers* (n = 82): hospitalized men with a confirmed diagnosis of alcoholism, positive score on MALT *Controls* (n = 70): hospitalized men who were clearly neither alcohol abusers nor alcoholics	GGT AST MCV	≥28 IU/L ≥18 IU/L ≥96 fL	78 48 73	67 91 60
Monteiro 1985[23]	*Drinkers* (n = 70): patients entering an ambulatory program for alcoholics, CAGE >2 *Controls* (n = 63): nonalcoholic healthy subjects	GGT AST MCV	>28 IU/L >18 IU/L >95 fL	64 55 51	86 84 63
Skinner 1984[24]	*Drinkers* (n = 68): ambulatory patients with known alcohol problems, consumption >400 g alcohol per week in previous 6 months *Controls* (n = 68): social drinkers, consumption <95 g alcohol per week, and ≤27 g alcohol per occasion	GGT MCV	M >51 IU/L F >33 IU/L >96 fL	39 49	94 99

GGT denotes gamma-glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MCV, mean corpuscular volume; MALT, Munich Alcoholism Test; CAGE, an acronym based on initial key words in 4-item alcoholism screening questionnaire.

have emerged as the most sensitive available laboratory markers.[10,16]

Studies on the value of the laboratory markers mentioned above have not always revealed satisfactory data. The aim of the present study is to review the value of the most commonly available laboratory tests (GGT, MCV, AST, AST/ALT ratio) used for the screening and recognition of problem drinkers in family practice. We offer opinions about how useful the laboratory tests are for the screening and recognition of problem drinkers.

Methods

Literature Search

Studies that were published from January 1984 to January 1993 were searched using the MEDLINE database. The major key word used was *alcoholism*. The subheadings were *enzymology*, *blood*, *diagnosis*, *classification*, *epidemiology*, and *physiopathology*. This search yielded a few hundred publications from each year. Articles relevant to this study were selected based on abstract information. Summaries in *Exerpta Medica*[17] were also checked for relevant publications. Cited references in the studies were included in this study if they were published no earlier than 1980.

For the tables, studies were selected in which the sensitivity as well as the specificity of the laboratory tests was presented or could be calculated. As a consequence, studies without a control group were excluded. Only data on GGT, MCV, AST, and the AST/ALT ratio are presented in the Tables, as they have emerged as the most sensitive tests associated with chronic excessive alcohol intake, and are easily accessible to family physicians.

Table 2. Laboratory Tests in Unselected General Practice Populations

Primary Author/Year	Population Under Study, Positivity Criterion, Number, and Prevalence	Test	Positivity Criterion	Sensitivity, %	Specificity, %
Baxter 1980[25]	Alcoholism is based on consumption data and on medical history (alcohol diagnosis).	GGT	M >40 IU/L F >25 IU/L	44	84
	Consumption data are based on a structured interview.	MCV	>97 fL	16	92
	Excessive drinking is defined as consuming >80 g alcohol per day or binge drinking >120 g alcohol by a regular consumption of >40 g.	AST	>30 IU/L	10	99
	n = 202; prevalence is 25.7%.				
Skinner 1984[24]	Consumption data are based on a self-administered medical-history questionnaire.	GGT	M >51 IU/L F >33 IU/L	33	89
	Excessive drinking is defined as consuming >60 g alcohol per day for at least 6 months.	MCV	>96 fL	25	94
	n = 61; prevalence is 15%.				
Poupon 1989[26]	Consumption data are based on an interview.	GGT	>40 IU/L	52	80
	Excessive drinking is defined as consuming >80 g alcohol per day for at least 2 years.	MCV	≥98 fL	32	91
	n = 173; prevalence is 11.7%.				
Nalpas 1989[27]	Consumption data were evaluated by using a standard questionnaire.	GGT	≥30 IU/L	50	81
	Excessive drinking is defined as consuming >80 g alcohol per day.	MCV	≥98 fL	27	91
	n = 303; prevalence is 11.2%.				

GGT denotes gamma-glutamyl transferase; MCV, mean corpuscular volume; AST, aspartate aminotransferase.

Analysis

In the analysis, a distinction was made between studies with selected populations of drinkers (Table 1) and studies in nonselected family practice populations (Table 2). The studies listed in Tables 1 and 2 are compared on the basis of four criteria: the population under study, the assessment of the alcohol consumption, the criteria concerning the amount of alcohol consumed, and the assay procedure (blood samples and laboratory tests).

The studies in Table 1 were compared with the studies in Table 2 by ranges in sensitivities and specificities of laboratory tests. The results are shown in Tables 3 and 4. Calculation of pooled estimates was not allowed, because of the heterogeneity of the studies. In addition, the predictive values for the studies in family practice populations are calculated for prevalences of problem drinking of 10% and 30% (Table 4).

In the figures, the prevalence (prior probability) is plotted against the posterior probability of problem drinking for subjects with a positive test result (positive predictive value) and for subjects with a negative test result (1− negative predictive value), using Bayes' theorem.

Table 3. Ranges of Sensitivity and Specificity of Laboratory Tests in Selected Patient Populations

Test	Sensitivity, %	Specificity, %
GGT	39–90	37–94
MCV	25–87	60–99
AST	48–69	68–91
AST/ALT >1	69–87	46–85
AST/ALT >2	19	96

NOTE: Data are based on studies outlined in Table 1.[18–24]
GGT denotes gamma-glutamyl transferase; MCV, mean corpuscular volume; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Results

The studies of selected groups (Table 1) enable the determination of the optimal value of the sensitivity by carefully selecting alcoholic patients. Data from various groups of nonalcoholics can be used to establish the specificity of the tests. Because the selected groups are not representative of an existing population, the calculation of the predictive values is of minor importance. Predictive values are therefore not given in Table 1.

In the studies of family practice patients (Table 2), a defined criterion divides the population under study into a drinkers group and a control group. In these studies, data on the prevalence of problem drinking in the population under consideration are available. In combination with the sensitivity and the specificity of the test marker, it is possible to estimate the positive and negative predictive values of the tests under study.

The studies in Tables 1 and 2 differ in many respects, including the type of population, the assessment of alcohol consumption, the criteria for the amount of alcohol consumed, and the assay procedures (blood samples and laboratory tests).

Table 4. Diagnostic Performance of Laboratory Testing for the Screening and Recognition of Alcohol Abuse

Test	Sensitivity, %	Specificity, %	Prevalence, %	Positive Predictive Value, %	Negative Predictive Value, %
GGT	33–52	81–89	10	22–25	92–94
			30	53–56	76–80
MCV	16–32	91–94	10	19–32	91–92
			30	46–64	72–76
AST	10	99	10	11	91
			30	81	72

NOTE: *Data are based on the studies outlined in Table 2.*[24–27]
GGT denotes gamma-glutamyl transferase; MCV, mean corpuscular volume; AST, aspartate aminotransferase.

Population Under Study

In Table 1, subjects newly admitted to inpatient or outpatient alcoholism treatment units were usually included in the drinkers groups. Additional criteria for inclusion were the amount of alcohol consumed[18,20,21,24] and a positive score on a validated alcohol questionnaire.[22,23] In one study, patients with multiple drug abuse were excluded.[18]

In the studies mentioned in Table 1, various control groups were selected, eg, social drinkers[24] and healthy volunteers,[21] nonalcoholic hospitalized patients,[22] patients with various nonalcoholic liver diseases such as primary biliary cirrhosis and chronic active hepatitis,[18–21] and abstinent alcoholics.[19] In one study, drinkers and controls were matched according to sex, socioeconomic status, and smoking habits.[23] The values for the specificity presented in the tables are based on pooled data of the various control groups. Only the data presented in the study of Kapur et al[20] allow the estimation of the specificities for each of the control groups. γ-Glutamyl transferase levels were elevated in 82% of the patients with nonalcoholic liver diseases, whereas only 12% of the patients without liver disease showed elevated GGT values. None of the patients with nonalcoholic liver disease had an AST/ALT ratio >2. The specificities for MCV for patients with nonalcoholic liver disease and patients without liver diseases were high (89% and 97%, respectively).[20]

In the studies in Table 2, family practice patients were recruited consecutively over a limited period. The number of patients who refused to participate was not mentioned in these studies.

Assessing Problem Drinking

Admission to inpatient or outpatient alcohol treatment units was the predominant criterion for the studies in Table 1 to be included in the drinkers group. Additional criteria were consumption levels and a positive score on a validated alcohol questionnaire (CAGE, MALT). Most studies in Table 1 did not detail their assessment procedure.

In the studies in Table 2, the amount of alcohol consumed was used to divide the population into a drinkers group and a control group. All studies rely on the patient's self-report. In the majority of the studies mentioned in Table 2, alcohol consumption was assessed by an interview, conducted either by the family physician[26] or by researchers.[25] In a few studies, a standardized self-administered questionnaire was used.[27]

In the studies analyzed in Table 2, data on alcohol consumption were taken as a standard against which the laboratory tests were judged. Self-reports on consumption can be accurate, depending on the interview conditions.[28] Relying on consumption levels has its shortcomings, however, as there is a considerable variation in the level of alcohol consumption that leads to abuse or dependence. From a physiological point of view, the criteria for excessive drinking should be different for men and women.[29] The studies mentioned in the tables did not make this distinction. It is important to note that none of the studies cited in Table 2 used reliable and valid criterion measures for alcohol abuse and dependence, as for example the Diagnostic Interview Schedule and the Composite International Diagnostic Interview, based on DSM-III criteria.[30,31]

Criteria for Alcohol Consumption

The consumption criteria for the drinkers group in the studies in Table 1 vary from 50 to 200 g of alcohol per day.[18,19] The actual mean daily alcohol consumption in the drinkers group was mentioned in only two studies (Table 1), with the mean being 2 to 4 times higher than the formal criterion.[19,24] In the studies listed in Table 2, patients were included in the drinkers group if they reported a consumption of over 60 to 80 g of alcohol per day.[24–27] The actual mean daily alcohol consumption is about 1.5 times higher than the formal criterion set for the study.[26,27]

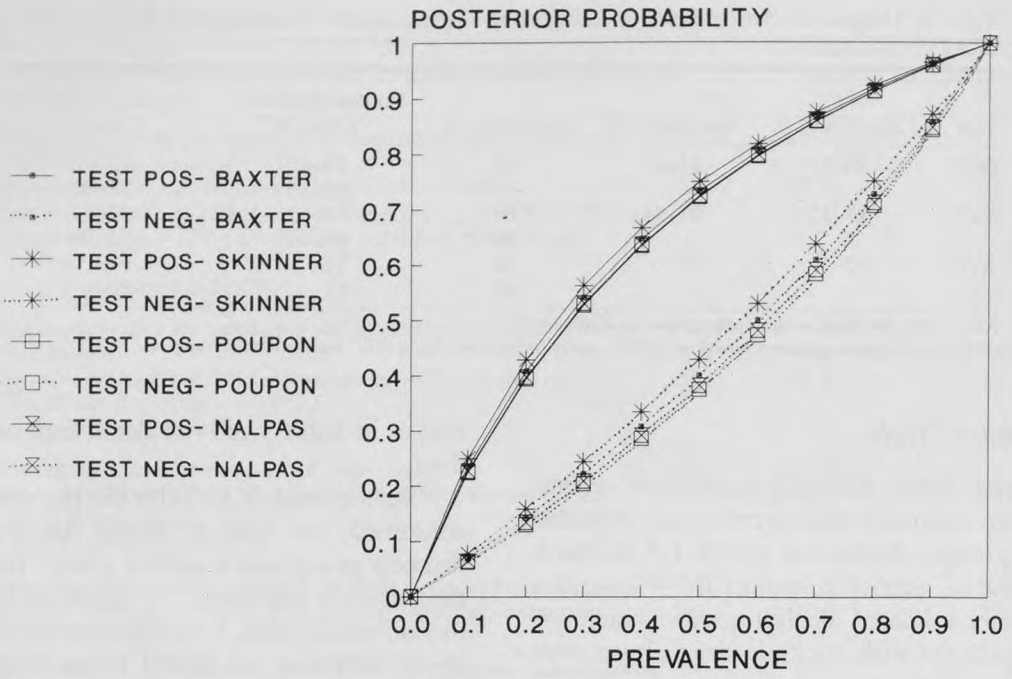

Figure 1. Posterior probability of problem drinking, given a positive or negative γ-glutamyl transferase test value at varying prevalences. Based on data reported in studies by Skinner,[24] Baxter,[25] Poupon,[26] and Nalpas.[27]

In the studies included in Table 1, an upper limit on the daily alcohol consumption of the subjects in the control groups was set, varying from 7 to 40 g.[19,21] In the studies in Table 2, the control group included subjects with a daily alcohol consumption of less than 60 to 80 g. For men, the limits in the studies in Table 2 were set in agreement with other limits used in the literature for harmful alcohol consumption.[16] For women, usually lower limits for what defines harmful alcohol consumption are used in the literature. In one study, family physicians indicated that, in general, consumption levels of 40 to 60 g of alcohol per day were a reason for intervention.[32]

Blood Samples and Laboratory Tests

Blood samples of the drinkers in most of the studies in Table 1 were taken at admission,[18] but not later than 3 days after the last alcohol intake.[19] In two studies in Table 2, blood samples were collected after an overnight fast.[26,27]

The upper reference values of the laboratory tests are subject to much variation, as is shown in Tables 1 and 2. In some studies for GGT, different reference values for men and women were used.[24,25] Reported upper limits for GGT range from 28 IU/L[22,23] to 100 IU/L.[18] Upper reference values for AST values ranged from 18 to 40 IU/L. The AST/ALT ratio was studied with a value exceeding 1 or 2 determining the positivity criterion. Upper limits for MCV ranged from 90 to 100 fL.[18,19]

Ranges

The ranges of the sensitivity and specificity of each of the laboratory tests are shown in Table 3 (based on the studies listed in Table 1) and in Table 4 (based on the studies listed in Table 2). In the nonselected family practice populations (Table 4), sensitivities were found to be lower (more false negatives) and specificities were found to be higher (fewer false positives).

Predictive Values

The predictive values of the tests for the family practice populations are shown in Table 4 and in Figures 1 and 2. In Table 4, the positive and negative predictive values were calculated for prevalences of problem drinking at 10% and at 30%. Figure 1 (GGT) and Figure 2 (MCV) show the increase of the posterior probability of disease with increasing prevalence from data in the studies listed in Table 2.[24–27] It can be seen in Figures 1 and 2 that the prevalence of problem drinking in the population under study has an important impact on the predictive values. The positive predictive value increases with increasing prevalence, while the negative predictive value decreases.

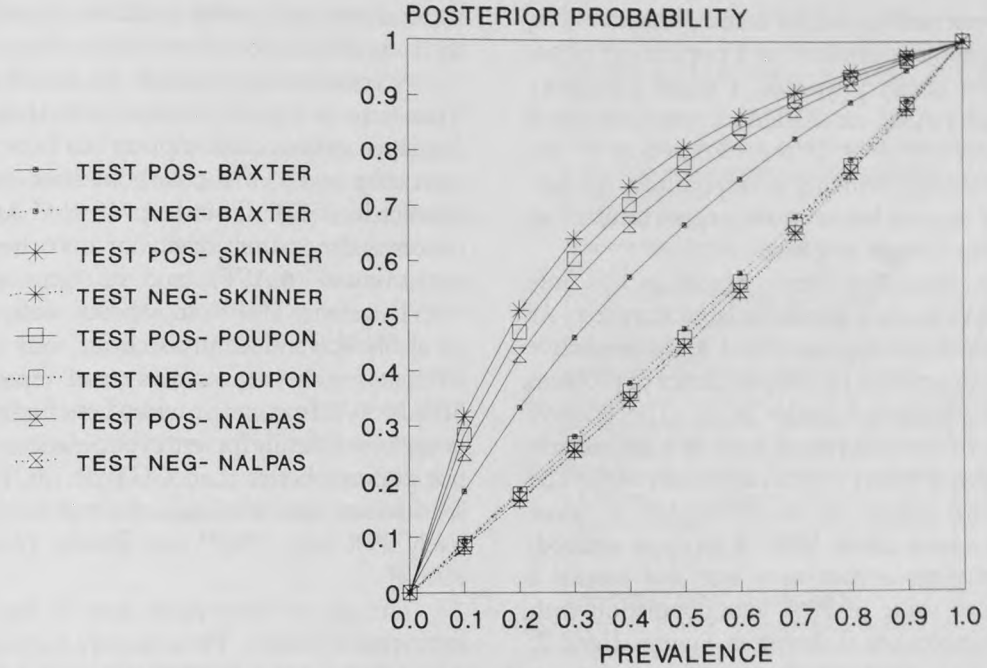

Figure 2. Posterior probability of problem drinking, given a positive or negative mean corpuscular volume test value at varying prevalences. Based on data reported in studies by Skinner,[24] Baxter,[25] Poupon,[26] and Nalpas.[27]

The predictive values for the various studies show great similarity, except for the positive predictive value of MCV.

Discussion

The studies listed in Tables 1 and 2 differ in many respects. From a theoretical point of view, it can be argued that:

- a high limit for alcohol consumption in the drinkers group (selected group studies) favors a high value for sensitivity
- a low limit for alcohol consumption in the control group (selected group studies) favors a high value for specificity
- the higher upper-reference values for the laboratory tests yield a higher specificity, at the expense of the sensitivity
- a lower specificity should be expected if nonalcoholic liver diseases are included in the control group, because of more false positives.

These theoretical expectations cannot easily be demonstrated, however, possibly because the studies differ in more than one indicator. Another explanation points to the accessory causes of elevated laboratory values. There is only an indirect relationship between the excessive intake of alcohol and the increased value of the laboratory markers.[33] As a consequence, the increased test values can be caused by other factors as well. For the serum liver enzymes, a strong positive association has been shown with body mass index and total serum cholesterol.[34,35] A positive association is also mentioned for blood pressure; the use of barbiturates, opiates, and anticonvulsants; diabetes mellitus; liver, heart, and renal diseases; and malignancies.[14,36] A strong negative association is found for coffee consumption and physical activity.[34,35] Accessory causes of elevated MCV include reticulocytosis, folic acid deficiency, vitamin B_{12} deficiency, and nonalcoholic liver diseases.[14] In the studies mentioned in Tables 1 and 2, these accessory causes of elevated laboratory tests are not taken into account.

The inclusion of patients with nonalcoholic liver diseases in the control group might be responsible for the lower ranges of specificity in the selected population studies, when compared with the studies of the nonselected family practice populations (Tables 3 and 4). The lower ranges of sensitivity in the studies with nonselected populations might be explained by the lower actual mean alcohol consumption in the drinkers group, irrespective of the limits set for the study. In fact, the drinkers in the family practice populations are thought to be in an earlier stage of alcoholism,[27] with more false negatives expected.

The data presented in Tables 1 and 2 indicate that, for identifying problem drinkers in a population of patients visiting the family physician, a single laboratory test (GGT, MCV, AST, or AST/ALT ratio) is not a suitable instrument.[8,20,37,38] If the recognition of the early stages of problem drinking is emphasized, the laboratory tests will be even less informative, as a result of an increasing number of false negatives.

What, then, should a family physician conclude from an elevated value on a particular laboratory test? As is shown in Table 4 and Figures 1 and 2, the predictive values are highly dependent on the prevalence of problem drinking in the population under study. The positive predictive value of the laboratory tests in a population with 10% problem drinkers is generally under 50%. The negative predictive values are usually higher, in some studies reaching values above 90%. It must be realized, however, that tossing a coin as a test also reveals a negative predictive value of 90% in a population with 10% problem drinkers. As is shown in Figures 1 and 2, the diagnostic gain is greater in the case of a positive test result, compared with the diagnostic gain of a negative test result, for the whole range of prevalences.

If a laboratory test is performed in cases in which problem drinking is suspected, the family physician is dealing with a subpopulation of patients, possibly with a higher prevalence of problem drinking. The positive predictive values increase, although they usually do not exceed 60% in a population with 30% problem drinkers. Accordingly, the negative predictive values decrease. But even if the prevalence is 80% (eg, in a population of patients scoring positively on an alcohol questionnaire), the positive predictive value of a laboratory test will usually not exceed 92%. We conclude that a positive test result does not confirm problem drinking, not even in cases of a strong suspicion of problem drinking. Thus, a positive test should be regarded as one of several nonspecific signs of problem drinking. The prevalence of problem drinking in the population under study should be taken into consideration when estimating the diagnostic gain of performing the laboratory test.

Although no single laboratory test marker is suitable for the identification of problem drinkers, usually combinations of abnormal laboratory values are thought to carry more weight.[8,14] However, only a slight improvement of diagnostic accuracy was shown to be present if GGT and MCV were used in combination.[23,39] The application of logistic regression or discriminant function analysis to combinations of biological markers has been demonstrated to have potential utility,[22,40–42] although Beresford et al[43] have concluded that "none of the discriminant laboratory functions gave recognition rates greater than chance alone." As yet, these (expensive) methods are not readily available in daily practice, and their use should not be recommended.

Several new test markers are currently under study. Transferrin is a glycoprotein involved in iron transport. Excessive alcohol consumption has been associated with increasing levels of the carbohydrate-deficient form of transferrin (CDT; Tf-index).[8,19–21,44] Another new test concerns the serum activity of mitochondrial aspartate transaminase (mAST), and its ratio with total AST (tAST) activity.[11,21,37] In studies with selected groups of alcoholics and controls, both tests appeared to be efficient, with sensitivities and specificities above 80%.[19–21,37] In contrast with these findings however, in nonselected family practice populations both tests did not perform better than GGT or MCV.[26,27] Reported sensitivities and specificities for mAST/tAST are respectively 29% and 77%,[27] and for the Tf-index, 45% and 89%.[26]

The use of laboratory tests is also mentioned in intervention studies. These studies focus on the effectiveness of interventions for problem drinkers in different settings, among which is family practice. Laboratory tests can be used as inclusion and outcome indicators and as monitoring instruments in the intervention.

Although some studies rely on GGT as the main inclusion criterion,[45,46] most of the intervention studies use patients' reports on alcohol consumption as the main entrance criterion,[47,48] or a combination of laboratory tests and consumption levels.[49–51] Because of the high number of false positives expected, other explanatory causes for an elevated GGT value should be considered carefully. Validated alcohol questionnaires were not used as inclusion indicators in any of the intervention studies.

In the intervention studies, changes in GGT values were used in discussions with patients in a feedback approach.[45,46,50,51] It was shown that GGT is a powerful motivating factor for changes in drinking habits among early stage risk drinkers.[50] Because reliance on self-reported alcohol consumption as the principal outcome measure is an important methodological problem in intervention studies, usually also an objective test marker, eg, GGT, was used as an outcome indicator.[45–48,50–52] A significant decrease in GGT values in the intervention group was already shown after an 8-week intervention period.[52] When patients were not included in the study because of their elevated GGT values, however, a significant decrease in mean GGT values was difficult to achieve.[48] It should be considered that reductions in GGT level to some extent could be attributed to the regression of the mean phenomenon.

The data presented in this paper indicate that guidelines for the recognition of problem drinking in family practice may use elevated laboratory test values as an

"alerting factor" for problem drinking, but not as confirmation of a suspicion. The excessive use of alcohol, as one of the possible causes for the elevated test value, should be discussed with the patient in an open and nonaccusatory way. Validated alcoholism questionnaires can be completed either by the patient or by health care personnel during a brief interview with the patient. Such questionnaires are more efficient than the laboratory measures as screening strategies.[9,43,53,54] However, no single screening procedure is completely satisfactory for the (early) recognition of problem drinking. Self-report measures, brief interview techniques, and laboratory tests should optimally be combined in the process of identifying problem drinkers. Moreover, the confirmation of the excessive use of alcohol in an interview with the patient is a prerequisite for a successful intervention.

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